# ELECTROLYTE CONTENT OF BLISTER FLUID IN PEMPHIGUS

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The electrolyte content of the serum and cell phase of the blood from patients with pemphigus has been reported in recent publications from this laboratory (1, 2). The serum sodium, chloride, calcium and protein was frequently found to be decreased; the degree of reduction corresponded to the severity of the clinical condition and the amount of skin involved. The concentration of the sodium in the red blood cells also showed a correlation with the clinical state of the patient; it was increased during exacerbations and normal or subnormal during remissions. These studies have been extended and in this communication determinations of the chemical constituents in the blister fluid from eleven patients with pemphigus vulgaris are reported.

## REVIEW OF THE LITERATURE

Few analyses of bullous fluid have been reported in the literature. Most of them have been made on cantharides blisters. Gänsslen (3, 4, 5) determined the non-protein nitrogen content of cantharides blisters in 245 normal persons, and found a close correlation with the non-protein nitrogen content of the blood serum. The values reported varied between 25 and 50 mgm. per 100 cc. The concentration of sugar in the fluid of cantharides blisters was found in 300 normal individuals to be slightly below the level of the blood sugar, namely 65 to 111 mgm. per 100 cc. Gänsslen further determined the sodium chloride content of cantharides blisters in 182 normal individuals. In all cases the concentration of sodium chloride was greater in the blister fluid than in the serum. In the blister fluid the values for sodium chloride varied between 500 and 650 mgm. per 100 cc., in the blood serum between 400 and 500 mgm. per 100 cc.

Urbach (6) studied the sodium chloride content of blister fluid in three persons. The blisters were produced by cantharides, burning and ultraviolet rays respectively, and contained 6 to 7 per cent more sodium chloride than did the blood serum. In a blister produced by cantharides the non-protein nitrogen was 39 as compared with 30 mgm. per 100 cc. in the blood serum.

Pitts and Johnson (7) determined the concentration of sodium, potassium and calcium in the blood serum and the fluid of cantharides blisters in normal persons and in patients with cancerous and non-cancerous diseases. There were no distinct differences between the various groups. All three constituents were found to be on the average lower in the blister fluid than in the blood serum. In the blood serum the average value for sodium was 337.9 mgm., for potassium 20.6 mgm. and for calcium 11.2 mgm. per 100 cc. In the blister fluid the average value for sodium was 331.0 mgm., for potassium 18.3 mgm., and for calcium 9.0

mgm. per 100 cc. Expressed in percentages, the concentration of sodium in the blister fluid was 98 per cent of that of the blood serum, of potassium 89 per cent and of calcium 80 per cent of that of the blood serum.

Harpuder and Schiering (8) determined the concentration of calcium in 23 cantharides blisters. The values varied between 8.0 and 10.5 mgm. per 100 cc. The average value was 9.1 mgm. per 100 cc. The authors did not determine the concentration of calcium in the blood serum in these cases, but they state that the values of calcium which they obtained in blister fluid were approximately the same as those encountered in normal blood sera.

Perutz and Klein (9) examined the fluid of 13 blisters, of which 8 were spontaneous and 5 were cantharides blisters. No analyses of blisters from pemphigus patients were included. In each patient the protein was lower than in the blood serum (65 per cent), and the chloride higher (108 per cent). In 2 blisters the sodium was determined and found to be lower than in the blood serum (96 per cent). The carbon dioxide content in 4 blisters was 25 per cent less than that of the blood serum. The authors stated that the difference in the concentration of electrolytes in blood serum and blister fluid can be accounted for by Donnan's law of membrane equilibrium.

Cornbleet (10) repeated Perutz' experiments. He examined the content of 17 cantharides blisters and of 2 spontaneous blisters, of which one was a dermatitis herpetiformis blister and the other a burn blister. He found the average protein content of both the artificial and spontaneous blisters only 63 per cent that of the blood serum. He confirmed Perutz' observation that in the blister fluid the chloride concentration was slightly higher and the sodium concentration slightly lower than in the blood serum. The average chloride content of blister fluid was 103 per cent and the sodium content 96 per cent of that of the blood serum. Cornbleet agreed with Perutz and Klein that the difference in concentration in bullous fluid and blood serum was in conformity with the Donnan equilibrium.

Chemical determinations of pemphigus blister fluid have been reported only by Urbach (11). He found in two patients the sodium chloride higher in the blister fluid than in the serum (104 and 106 per cent, respectively).

## RESULTS

The amount of sodium, potassium, calcium, total fixed base, chloride, phosphate, protein and non-protein nitrogen was determined in blister fluid and in blood serum of 11 patients with pemphigus vulgaris. The blister fluid and blood serum were collected on the same day in most patients. The chemical data are presented in Table I. In Table II the ratios of blister fluid and blood serum are given. The protein was lower in the blister fluid in all but one instance (case 1). Similarly, the calcium was lower in the blister fluid in all cases except one (case 2). The other constituents varied in regard to their relative concentration in blister fluid and blood serum; they were higher in the blister fluid in some cases and lower in others. It was noted, however, that there was a correlation between the ratios blister fluid/blood serum for sodium and for chloride on one side,

TABLE I

*Concentration of constituents of bullous fluid and blood serum from patients with pemphigus vulgaris*

| | | | | | | M.EQ. PER LITER | | | | MGM. PER 100 cc. | | GM. PER LITER | M.EQ. PER LITER |
|---|---|---|---|---|---|---|---|---|---|---|---|---|---|
| | | | | | | Total base | $Na^+$ | $Cl^-$ | $K^+$ | $PO_4^-$ | NPN | $Prot^-$ | $Ca^{++}$ |
| 1 | Pemph. vulg. acutus | S. C. | + | 10-14-38 | bli. | | 127.0 | | **7.46** | | | | |
| | | | | 10-18-38 | ser. | | **137.6** | | 3.82 | | | | |
| | | | | 10-28-38 | bli. | 140.7 | 130.7 | | **5.49** | | **39.8** | **4.34** | |
| | | | | 10-27-38 | ser. | **144.7** | **132.5** | | 4.51 | | 32.5 | 4.25 | |
| 2 | | U. B. | + | 4-27-39 | bli. | | 140.0 | 95.1 | **5.50** | **4.40** | **35.0** | 5.28 | **4.76** |
| | | | | 4-27-39 | ser. | | **140.4** | **104.1** | 3.97 | 3.72 | 28.0 | **5.71** | 4.68 |
| 3 | | N. P. | + | 10-10-40 | bli. | 139.5 | 130.8 | 97.5 | **5.86** | **5.15** | **39.7** | 5.21 | 3.97 |
| | | | | 10-11-40 | ser. | **154.0** | **142.6** | **102.6** | 5.05 | 4.16 | 32.0 | **6.28** | **4.50** |
| 4 | Pemph. vulg. chron. | G. B. | L | 5-11-38 | bli. | **155.0** | 144.8 | **107.4** | 3.24 | 3.30 | | 4.52 | |
| | | | | 5-10-38 | ser. | 153.7 | 144.0 | 100.8 | 3.33 | 3.23 | | **7.10** | |
| 5 | | C. M. | (+) | 10-31-38 | bli. | **150.5** | **139.6** | **111.4** | 4.63 | 4.56 | 37.8 | 2.73 | 3.62 |
| | | | | 10-31-38 | ser. | 147.4 | 137.4 | 105.2 | **4.90** | **4.79** | 37.1 | **4.93** | **4.23** |
| | | | | 11-10-38 | bli. | **148.8** | | **106.4** | 4.23 | 5.25 | 40.1 | | |
| | | | | 11- 9-38 | ser. | 147.3 | | 100.0 | **4.86** | **9.82** | **43.0** | | |
| 6 | | F. M. | + | 2- 8-39 | bli. | 150.5 | | **107.9** | 4.16 | | | 3.82 | |
| | | | | 2- 8-39 | ser. | 151.5 | | 102.4 | 4.16 | | | **6.83** | |
| 7 | | I. W. | L | 9-23-39 | bli. | | | | | | | 4.86 | |
| | | | | 9-23-39 | ser. | | | | | | | **6.36** | |
| 8 | | E. S. | L | 3-12-40 | bli. | 151.5 | 142.5 | **110.7** | 4.29 | 1.82 | 25.8 | 3.25 | 3.57 |
| | | | | 3-12-40 | ser. | 151.0 | 140.7 | 105.5 | 4.42 | 2.00 | 26.0 | **5.34** | **4.26** |
| | | | | 5- 4-40 | bli. | | **144.6** | | | | 29.0 | 4.73 | |
| | | | | 5- 4-40 | ser. | | 136.3 | | | | 29.0 | **6.01** | |
| 9 | | J. L. | L | 3-22-40 | bli. | 151.0 | **143.4** | **109.9** | 4.20 | 2.87 | 16.7 | 4.20 | 3.62 |
| | | | | 3-22-40 | ser. | 151.5 | 137.9 | 107.3 | 4.00 | **3.50** | **18.8** | **6.89** | **4.39** |
| | | | | 5- 9-40 | bli. | | **143.0** | | | | 2.02 | 5.23 | 4.10 |
| | | | | 5- 9-40 | ser. | | 133.0 | | | | **23.2** | **7.29** | **4.81** |
| | | | | 6- 5-40 | bli. | 149.0 | 138.2 | **110.1** | 3.80 | 1.25 | 19.0 | 4.17 | 3.69 |
| | | | | 6- 5-40 | ser. | 147.5 | 136.5 | 106.3 | **4.20** | **2.65** | 19.0 | **6.15** | **4.12** |
| 10 | | A. J. | L | 6-20-40 | bli. | | 137.3 | | | | **33.5** | | 4.33 |
| | | | | 6-20-40 | ser. | | 135.6 | | | | **38.0** | | **4.66** |
| | | | | 8-24-40 | bli. | **165.0** | **141.5** | | | | | 5.22 | 6.41 |
| | | | | 8-24-40 | ser. | 142.5 | 132.2 | | | | | **6.40** | **7.53** |
| 11 | | K. S. | L | 9-11-41 | bli. | | 146.5 | | | | | | |
| | | | | 9-11-41 | ser. | | 145.3 | | | | | | |

The normal concentrations of the various constituents of the blood serum are indicated in Table III.

Explanation of signs: + patient died of pemphigus; (+) patient died of causes other than pemphigus; L patient living.

and the ratios for potassium, for phosphate and for non-protein nitrogen on the other side. Namely, whenever the chloride was higher in the blister fluid than in the blood serum, the sodium was also higher and the potassium, phosphate and

non-protein nitrogen were lower (cases 1 to 3). On the other hand, whenever the chloride was lower in the blister fluid than in the blood serum, the sodium was also lower and the potassium, phosphate and non-protein nitrogen were higher (case 4 to 9). This close correlation between the ratios for sodium and for chloride in the pemphigus blister fluid is in contrast to the findings of Perutz (9) and Cornbleet (10) who had observed in cantharides blisters consistently a ratio of above 1.0 for chloride and below 1.0 for the sodium.

The protein ratio in the blister fluid was highest in the three patients in whom the sodium and chloride was lower in the blister fluid than in the blood serum,

TABLE II

*Comparison of the concentrations of various constituents in bullous fluid and in blood serum by means of the ratio of bullous fluid to blood serum*

| | RATIO $\frac{\text{BLISTER FLUID}}{\text{BLOOD SERUM}}$ OF | | | TOTAL BASE | $Na^+$ | $Cl^-$ | $K^+$ | $PO_4^-$ | NPN | PROT$^-$ | $CA^{++}$ |
|---|---|---|---|---|---|---|---|---|---|---|---|
| 1 | Pemph. | S. C. | 10-14-38 | | .92 | | 1.95 | | | | |
| | vulg. | | 10-27-38 | **.97** | **.98** | | **1.22** | | **1.22** | **1.02** | |
| | acutus | | | | | | | | | | |
| 2 | | U. B. | 4-27-39 | | 1.00 | **.91** | **1.38** | **1.32** | **1.25** | **.93** | **1.02** |
| 3 | | N. P. | 10-10-40 | **.91** | **.92** | **.95** | **1.16** | **1.24** | **1.24** | **.83** | **.95** |
| 4 | Pemph. | G B. | 5-10-38 | 1.01 | 1.01 | **1.07** | .97 | 1.02 | | **.64** | |
| 5 | vulg. | C. M. | 10-31-38 | **1.02** | **1.02** | **1.06** | **.94** | .95 | 1.02 | **.56** | **.86** |
| | chron. | | 11- 9-38 | 1.01 | | **1.06** | **.87** | **.54** | **.93** | | |
| 6 | | F. M. | 2- 8-39 | .99 | | **1.05** | 1.00 | | | **.56** | |
| 7 | | I. W. | 9-23-39 | | | | | | | **.77** | |
| 8 | | E. S. | 3-12-40 | 1.00 | 1.01 | **1.05** | .97 | **.91** | .99 | **.61** | **.84** |
| | | | 5- 4-40 | | **1.06** | | | | 1.00 | **.79** | |
| 9 | | J. L. | 3-22-40 | 1.00 | **1.04** | **1.02** | 1.05 | **.82** | **.89** | **.61** | **.82** |
| | | | 5- 9-40 | | **1.07** | | | | **.87** | **.72** | **.85** |
| | | | 6- 5-40 | 1.01 | 1.01 | **1.04** | **.91** | **.47** | 1.00 | **.68** | **.90** |
| 10 | | A. J. | 6-20-40 | | 1.01 | | | | **.89** | | **.93** |
| | | | 8-24-40 | **1.16** | **1.07** | | | | | **.82** | **.84** |
| 11 | | K. S. | 9-11-41 | | 1.01 | | | | | | |
| Pemph. vulg. acutus (average)..... | | | | .94 | .96 | .93 | 1.43 | 1.28 | 1.24 | .93 | .98 |
| Pemph. vulg. chronicus (average)... | | | | 1.03 | 1.03 | 1.05 | .96 | .79 | .95 | .68 | .85 |

and the potassium, phosphate and non-protein nitrogen was higher (case 1 to 3), in these cases the average protein ratio was .93. In the other cases (case 4 to 10) the average protein ratio was .68.

In order to ascertain that the difference of values was not due to the difference in the amount of protein in serum and blister fluid, the ratio of blister fluid to blood serum was computed not only per unit of fluid, as in Table II, but also per unit of water, taking as water the weight of fluid minus the weight of protein. No essential change in the ratio of the various constituents was found by this computation.

The three patients with the low ratio of sodium and chloride and the high ratio

of potassium, phosphate and non-protein nitrogen in the blister fluid differed clinically from the other patients. In these three patients (case 1 to 3) the disease had started with severe, diffuse involvement of the mouth and lips; the cutaneous lesions consisted of flaccid blisters which broke easily and developed into erosions with a tendency to peripheral enlargement and with little or no tendency to heal; these three patients died of pemphigus within a few months (5, 6 and 7 months, respectively, after onset of the disease, and $1\frac{1}{2}$, $4\frac{1}{2}$ and $6\frac{1}{2}$ months, respectively, after appearance of cutaneous lesions). This form of pemphigus vulgaris was first recognized as a particularly malignant form by Brocq (12) who called it "pemphigus subaigu malin à bulles extensives." In previous communications this form has been called by the authors acute pemphigus (1) or pemphigus vulgaris acutus (2). The other 8 patients suffered from what has been called by us pemphigus vulgaris chronicus. Their cutaneous lesions consisted of tense bullae

TABLE III

*Normal values for various constituents of the blood serum and of the skin as given in the literature*

The values quoted for the blood serum represent the range of normal as obtained with the methods used in our laboratory (13)

| | M.EQ. PER LITER | | | MGM. PER 100 CC. | |
|---|---|---|---|---|---|
| | $Na^+$ | $Cl^-$ | $K^+$ | $PO_4^-$ | NPN |
| Blood serum | 139–141 | 102–106 | 4–5 | 3.1–4.5 | 20–35 |
| Human skin (figures calculated per kg. of wet skin for Na, Cl and K, per 100 grams of wet skin for $PO_4$ and NPN) | 55.7<br>68.5<br>55.2<br>Brown (14)<br>Brown (15)<br>Dörffel (16) | 64<br>74<br>Volk and Fantl (17)<br>Urbach (18) | 21.7<br>23.4<br>20.4<br>23.4<br>Brown (14)<br>Brown (15)<br>Nathan & Stern (19)<br>Dörffel (16) | 61<br>58<br>Brown (15)<br>Heubner (20) | 66<br>63–84<br>60–90<br>Nadel (21)<br>Urbach (22)<br>Kaplansky (23) |

which did not break as easily as the blisters in the acute form and the erosions showed no tendency to peripheral enlargement but rather a tendency to heal. Five of the seven patients showed oral lesions, which, however, were only few in number and, with one exception, appeared after the cutaneous lesions. Five of the seven patients are living although the disease began more than two years ago in every patient. One died of carcinoma of the prostate and only one of pemphigus, at an age of 78.

## DISCUSSION

It is believed to be significant that in the three patients with pemphigus vulgaris acutus the concentration of sodium and chloride was lower and the concentration of potassium, phosphate and non-protein nitrogen was higher in the bullous fluid than in the blood serum; whereas in patients with pemphigus vul-

garis chronicus the sodium and chloride were higher and the potassium, phosphate and non-protein nitrogen were lower in the blister fluid than in the blood serum.

This finding may be related to the fact that sodium and chloride are present in higher concentrations in the blood serum than in the skin, while potassium, phosphate and non-protein nitrogen are present in higher concentrations in the skin than in the blood serum. Average values of the amount of sodium, chloride, potassium, phosphate and non-protein nitrogen as found in the blood serum and in the human skin are tabulated in Table III.

It is suggested as a hypothesis that in pemphigus vulgaris acutus the bullous fluid is derived to a greater extent from the cutaneous tissue than in pemphigus vulgaris chronicus in which the blood serum supplies the greater amount.

## SUMMARY

1. The concentration of electrolytes in blister fluid and blood serum was determined in eleven patients with pemphigus vulgaris.

2. By comparing the amount of the various electrolytes in the blister fluid with the amount in the blood serum it was found that the protein and calcium were lower in the blister fluid than in the blood serum in all but one instance.

3. The amount of sodium, chloride, potassium, phosphate and non-protein nitrogen in the blister fluid was higher than in the blood serum in some, and lower in others. There was, however, a correlation between the ratios blister fluid/blood serum for sodium and for chloride on one side, and the ratios for potassium, for phosphate and for non-protein nitrogen on the other side. In the three patients with pemphigus vulgaris acutus the sodium and chloride were lower and the potassium, phosphate and non-protein nitrogen were higher in the blister fluid than in the blood serum. In the patients with pemphigus vulgaris chronicus the sodium and chloride were higher and the potassium, phosphate and non-protein nitrogen were lower in the blister fluid than in the blood serum.

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